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PATENT

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Applicant: Mc Donald et al. Examiner: QAZI, Sabiha Naim

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For: Method of Treatment of Cancer by Controlling Graft versus Leukemia Using Topical Active Corticosteroids

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents

Washington, DC 20231

Sir:

I, Robert N. Brey, Ph.D., hereby make the following declaration:

1. I received a Ph.D. degree from the University of Virginia in the year 1976.

2. I have been employed in the field of pharmaceutical and vaccine development since 1982 after completing postdoctoral studies at Massachusetts Institute of Technology. I have been employed at Genex Corporation in Gaithersburg Maryland from 1982 through 1985 as a Senior Scientist in Microbial

Product Development and Biochemistry, as Project Manager and Manager of Molecular Biology at Praxis Biologics (now Wyeth Vaccines) from 1985 to 1993 and since 1996 I have been employed by DOR Biopharma, Inc., of Lake Forest, IL, which owns assignee Enteron Pharmaceuticals, Inc. My current title is Chief Scientific Officer.

3. I have read the subject patent application and the rejection in the Office Action dated December 1, 2004. I am fully familiar with the field of technology embraced by this patent application.

4. The subject matter of this patent application has been proved in clinical studies in human cancer patients with hematologic malignancies. A randomized, prospective, double blind, placebo controlled, multi-center pivotal trial was conducted to evaluate beclomethasone dipropionate (BDP) as a treatment for graft versus host disease (GVHD) following hematopoietic stem cell transplant in blood-borne cancer patients receiving stem cell transplants. The data discussed in this Declaration was contained in an information package submitted to the U.S. Food and Drug Administration in support of a New Drug Application (NDA) for orBec® ORAL BECLOMETHASONE DIPROPIONATE TABLETS.

5. The BDP was formulated as two separate dosage forms for oral administration: an immediate release (IR) tablet and an enteric coated (EC) tablet. One hundred twenty-nine (129) patients were enrolled at 14 centers in the U.S. and 2 in France. Sixty-seven patients were randomized to placebo and 62 to BDP. Patients were at least 10 days post allogeneic hematopoietic cell transplantation, had gastrointestinal symptoms consistent with Grade II GVHD, and had endoscopic evidence of GVHD. The diagnosis of GVHD was confirmed by biopsy of the

intestine (esophagus, stomach, small intestine, or colon) or skin, when intestinal biopsy was contraindicated.

6. After being diagnosed with GVHD, patients were started on standard prednisone therapy. Patients were administered 2 mg/kg/day or 1 mg/kg/day for 10 days as a starting dose. After 10 days at this initial dose, prednisone was tapered over 7 days, after which the patients were maintained on a maintenance physiologic replacement dose of prednisone of 0.0625 mg/kg/day or 0.125 mg/kg/day. Patients received BDP at a dose of 2 mg four times daily, for a total dose of 8 mgs, or placebo for a maximum of 50 days, unless they met the treatment failure endpoint beforehand or withdrew from the study.

7. Patients were monitored at clinic visits for evidence of treatment failure. The primary efficacy endpoint was the time to treatment failure through study day 50. Treatment failure was defined as a worsening or recurrence of their GVHD of such degree as to require an increase in their immunosuppressive therapy. A subject was defined as a treatment failure if the patient required prednisone or equivalent IV corticosteroids at doses higher than that specified in the protocol in response to uncontrolled signs or symptoms of GVHD; or required additional immunosuppressant medications other than those permitted by the protocol (see below) in response to uncontrolled signs or symptoms of GVHD; or administered "open-label BDP" in response to uncontrolled signs or symptoms of GVHD. The time to treatment failure was calculated as the number of days elapsed between the randomization date and the date on which the subject was first identified as a treatment failure by the investigator. The number of days elapsed between two consecutive dates was considered to be one day.

8. Secondary efficacy endpoints included: 1) the time to treatment failure through study day 80, 2) the proportion of subjects who experienced treatment failure by study days 10, 30, 50, 60, and 80, and 3) Karnofsky performance status scores.

9. Safety was primarily assessed based on the following: 1) cumulative systemic corticosteroid exposure, 2) the incidence and degree of HPA axis suppression in patients who had not experienced treatment failure by study day 50, 3) rates of treatment-emergent adverse events, and 4) the overall survival rate 200 days post-transplant.

10. The primary analysis of the primary and secondary efficacy endpoints was based on the intent-to-treat principle. The analysis of the primary efficacy endpoint was based on the Kaplan-Meier method and log-rank test stratified by source of allograft (two HLA haplotype identical sibling – yes, no). Hypothesis tests of the primary and secondary efficacy endpoints were performed using a two-sided significance level of 0.05. No adjustments were made to the significance level for inferential tests of the secondary efficacy endpoints. All patients who received at least one dose of BDP or placebo were included in the assessment of safety.

11. Time to treatment failure

The primary efficacy endpoint of time to treatment failure through study day 50 is summarized by "treatment group" in Table 1. Also summarized is the secondary endpoint of time to treatment failure through study day 80. Although these endpoints overlap, the latter endpoint includes events that occurred during the 30-day post-treatment observation period and is intended to provide information on the

durability of effect following treatment discontinuation. The Kaplan-Meier estimates for each endpoint are displayed in Figures 1 and 2, respectively.

12. As shown in Figure 1, there was an initial increase in the treatment failure rate for patients in the BDP group compared to placebo during the first 10 days of study treatment. Eight patients in the BDP group met the treatment failure endpoint during this period compared to 4 patients in the placebo group. Shortly after the start of the prednisone taper, approximately 10 days post-randomization, a difference between the BDP and placebo groups emerged (in favor of the BDP group) and steadily increased throughout the remainder of the 50-day study treatment period, such that by study day 50, the cumulative treatment failure rate was 31% for BDP versus 48% for placebo (p=0.0515, Z-test).

13. During the 50-day study treatment period, the risk of treatment failure was reduced by 37% for patients in the BDP group relative to placebo (hazard ratio 0.63; 95% CI: 0.35, 1.37); however, the primary inferential comparison for this endpoint was not statistically significant (p=0.1177, stratified log-rank test). This comparison includes all treatment failures observed during the 50-day study treatment period, including the 12 events that occurred during the first 10 days of treatment when all patients were receiving high-dose corticosteroids (1-2 mg/kg/day). It should be noted that 44% of the total number of treatment failures for BDP occurred within the first 10 days of randomization and prior to the prednisone taper. This compares to 13% of the treatment failures for placebo during this same period.

14. The time to treatment failure through study day 80 was also evaluated to assess the durability of response, and includes treatment failures that occurred

during the 50-day study treatment period and 30-day post-treatment observation period. As shown in Figure 2. the emerging difference between treatment groups that was observed during the 50-day treatment period continued to increase throughout the 30-day post-treatment observation period such that the overall cumulative treatment failure rate by study day 80 was 39% for BDP versus 65% for placebo (p=0.0048, Z-test).

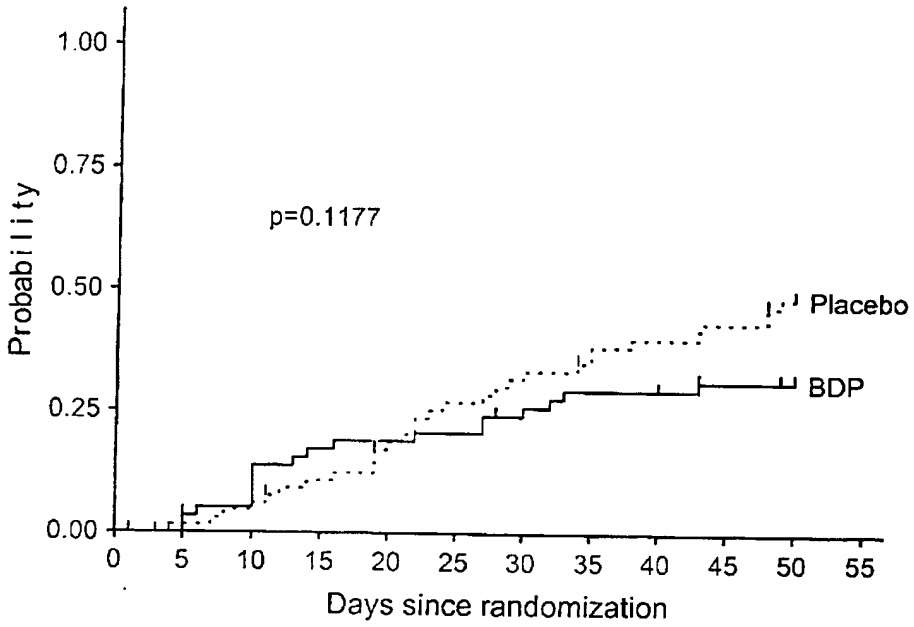
15. For the entire 80-day study period, the risk of treatment failure was statistically significantly reduced by 44% for patients in the BDP group relative to placebo (hazard ratio 0.56; 95% CI: 0.33, 0.94; p=0.0226, stratified log-rank test). In addition to the decreased risk, the median time to treatment failure was increased by more than 28 days for the BDP group compared to placebo.

Table 1: Results of Intent-to-Treat Analysis of the Time to Treatment Failure through Study Days 50 and 80 (All Randomized Subjects)

Endpoint	Treatment Group		P-value
	Placebo N=67	BDP N=62	
Time to treatment failure through Study Day 50			
Number with treatment failure	30	18	
Treatment failure rate by Study Day 50	0.48 (0.39, 0.60)	0.31 (0.23, 0.43)	0.0515
Median time to treatment failure (95% CI)	Not achieved	Not achieved	
Hazard ratio (95% CI)	0.63 (0.35, 1.37)		0.1177
Time to treatment failure through Study Day 80			
Number with treatment failure	39	22	
Treatment failure rate by Study Day 80	0.65 (0.55, 0.76)	0.39 (0.30, 0.52)	0.0048
Median time to treatment failure (95% CI)	52 days (35, 75)	Not achieved	
Hazard ratio (95% CI)	0.56 (0.33, 0.94)		0.0226

The hazard ratio was estimated from a univariate Cox proportional hazards model. Placebo serves as the reference group.

Figure 1: Time to Treatment Failure through Study Day 50 Estimates Based on Kaplan-Meier Method (All Randomized Subjects)

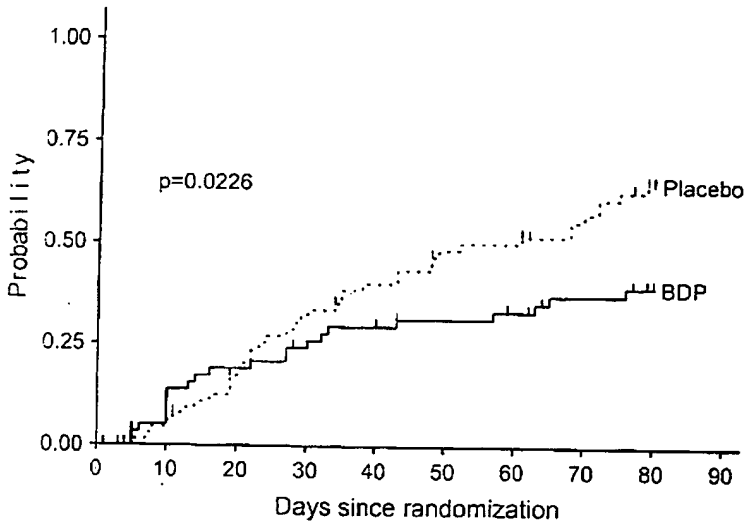


	1-10	11-20	21-30	31-40	41-50
BDP	8/62	3/50	4/47	2/42	1/39
Placebo	4/67	8/61	9/50	4/41	5/36

(#events/#at risk)

P-value is based on the stratified log-rank test. Significance level of 0.05 (two-sided).

Figure 2: Time to Treatment Failure through Study Day 80 Estimates Based on Kaplan-Meier Method (All Randomized Subjects)



	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
BDP	8/62	3/50	4/47	2/42	1/39	1/37	2/35	1/30
Placebo	4/67	8/61	9/50	4/41	5/36	1/30	4/29	4/23

(#events/#at risk)

P-value is based on the stratified log-rank test. Significance level of 0.05 (two-sided).

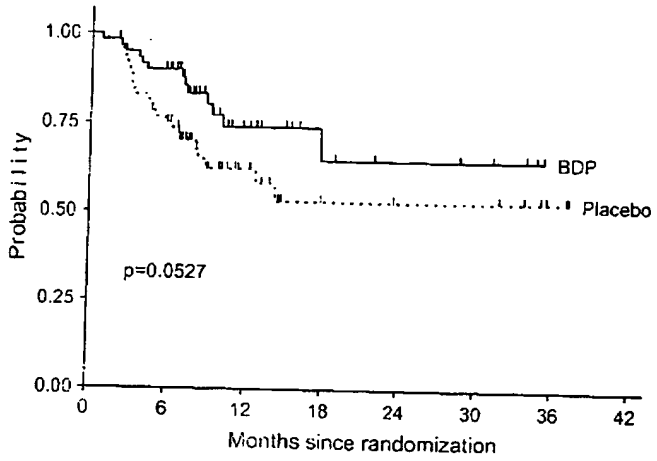
16. Overall survival

Treatment with BDP was associated with a statistically significantly higher overall survival rate 200 days post-transplant relative to placebo (p=0.006, Z-test). Based on Kaplan-Meier estimates, the overall survival rate 200 days post-transplant was 0.91 for the BDP group (95% CI: 0.66, 0.84) versus 0.74 for placebo (95% CI: 0.66, 0.84). The most common primary cause of death was relapse of the underlying malignancy, which occurred in 6 patients in the placebo group (9%) and in 2 patients in the BDP group (3%). The second most common cause of death appeared to be sepsis, however, the final determination is pending further investigation.

Based on a univariate time-dependent Cox proportional hazards model, the risk of mortality during this period was 68% lower following the initiation of treatment with BDP when compared to no treatment (hazard ratio 0.32; 95% CI: 0.12, 0.87; p=0.0252). A multivariate Cox model was used to evaluate the effect of BDP while simultaneously accounting for selected competing causes of mortality after hematopoietic cell transplant. The competing causes of mortality included the subject's age and gender, intensity of the conditioning regimen (ablative, non-ablative), primary diagnosis, transplant source (bone marrow, peripheral blood stem cells), and degree of HLA match. The results of the multivariate model are displayed in Table 2. With the exception BDP treatment (hazard ratio 0.32; 95% CI: 0.11, 0.89; p=0.0292), none of the factors included in the model were statistically significantly associated with the duration of survival during the 200-day period following transplant.

17. An exploratory analysis was also performed to evaluate the relationship between the treatment failure endpoint during the 80-day study period and duration of overall survival during the 200-day period following transplant. Based on a time-dependent Cox proportional hazards model, patients who experienced treatment failure during this period had a statistically significantly greater risk of death (due to any cause) during the 200-day post-transplant period relative to patients who did not experience treatment failure (hazard ratio 3.36; 95% CI: 1.36, 8.29; p=0.0085).

Figure 3. Duration of Overall Survival – Post-Randomization (Safety Population)



	0-6	7-12	13-18	19-24	25-30	31-36	37-42
BDP	6/61	6/54	1/17	0/7	0/5	0/4	0/0
Placebo	16/66	6/47	2/16	0/8	0/7	0/7	0/2

(#events/#at risk)

P-value is based on the log-rank test. Significance level of 0.05 (two sided).

Table 2: Multivariate Proportional Hazards Model for the Duration of Overall Survival 200 Days Post-Transplant (Safety Population)

Variable	Coefficient (b_i)	HR [exp(b_i)]	95% CI	P-value
BDP	−1.155	0.32	(0.11, 0.89)	0.0292
Males	0.225	1.25	(0.52, 3.03)	0.6174
Age (per 1-year increase)	0.016	1.02	(0.98, 1.05)	0.3496
Non-ablative conditioning regimen	0.207	1.23	(0.48, 3.19)	0.6705
2 HLA haplotype identical sibling	−0.758	0.47	(0.20, 1.09)	0.0793
Bone marrow as source of stem cells	−0.722	0.49	(0.06, 3.79)	0.4910
Primary diagnosis associated with an elevated risk of disease-related mortality	0.290	1.34	(0.48, 3.69)	0.5753

HR = hazard ratio; CI = confidence interval.
The hazard ratio for each variable was estimated from a multivariate Cox proportional hazards model.
The variable for BDP was defined in the model as a time dependent covariate, taking on a value of 1 during the period between randomization to BDP and death (or last follow-up if alive). Otherwise, the value of the variable was zero.

18. This study shows an improvement in outcome for all parameters measured in patients with intestinal GVHD treated with oral BDP. While the primary efficacy variable (time to treatment failure in the first 50 days post randomization) showed a clear trend towards efficacy, there was a clear-cut

statistical and clinically meaningful advantage over the first 80 days. The improvement in time to treatment failure was accompanied by a 69% relative reduction in mortality at 200 days post transplant, the prospectively defined survival endpoint.

19. There was a significant correlation between both treatment failure and corticosteroid exposure and survival. and a suggestion of mechanism as demonstrated by the decrease in deaths in the treatment group due to both infection and relapse of underlying disease (suggesting protection of graft-versus-leukemia effect with lower corticosteroid exposure).

20. In summary, this study showed that patients treated with a 10-day induction course of prednisone followed by a rapid prednisone taper and oral BDP, 2 mg four times daily for 50 days, have an improved outcome compared to patients treated with the same prednisone induction plus placebo, as measured by proportion of treatment failures at various time points, time to treatment failure to study day 80, as well as survival at transplant day 200. These improvements in outcome are achieved without an increase in clinically significant toxicity, yielding a favorable risk to benefit ratio.

21. An examination of the causes of death in the placebo arm (mostly infections and relapses of leukemia) provides a biologically plausible mechanism for better survival in the oral BDP group. Control of GVHD with an oral topical corticosteroid leads to less prednisone exposure, less systemic immunosuppression, fewer fatal infections, and possibly an enhanced graft-versus-leukemia (GVL) effect. There are data showing that the frequency of leukemic relapse after

allogeneic hematopoietic cell transplant is lower in patients who experience GVHD after transplant, a phenomenon called the GVL effect. We hypothesize that avoidance of prolonged prednisone exposure preserves the GVL effect, resulting in fewer relapses of leukemia. A multivariable Cox proportional hazards model, taking into account competing risk factors for mortality. for the duration of survival at day-200 post transplant shows that randomization to oral BDP leads to significantly less mortality (hazard ratio 0.32. 95% confidence interval 0.11-0.89, p=0.029) and improved survival.

22. Oral BDP appears to be extremely safe. The adverse event profile of oral BDP was little different from that of placebo, with the exception of biochemical evidence of greater suppression of the HPA axis at study day 50 in patients randomized to oral BDP, compared to placebo patients who had not received additional prednisone.

23. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: June 1, 2005

By: Robert N Brey

Robert N. Brey, Ph.D.